

HLA: The Compatibility Genes for Transplantation

The ability of the immune system to distinguish “self” from “non-self” is critical for fighting infection and controlling potentially cancerous cells. Simultaneously, the immune system must avoid targeting “self” tissue. Human leukocyte antigen (HLA) molecules are cell surface receptors that present peptide antigens to T-cells to mediate the adaptive immune response.

Through the antigen presentation pathway, HLA allows the immune system to assay both “self” and “non-self” proteins from inside the cell and the outside environment. The tension between pathogen evolution away from easy presentation by HLA molecules and the adaptive evolution of the potential host has created a number of different allele variants for HLA within the human population. There are over 13,000 known alleles of HLA Class I genes (HLA-A,B, and C) and 4,500 alleles of HLA Class II genes (HLA-DRB1, DQA1, DQB1, DPA1, and DPB1). The number of possible combinations for these HLA variants is so high that many of us have an HLA genotype that is unique. This potentially complicates processes that can be influenced by the immune response, most notably organ and tissue transplant.

The lab of **Loren Gragert** is studying ways to apply HLA-based matching criteria to organ transplants to improve patient outcomes.

Improving Matching Algorithms for Transplantation

Dr. Gragert previously worked for 12 years in the Bioinformatics Research department at National Marrow Donor “Be The Match” Program. This is the US registry that facilitates unrelated hematopoietic stem cell transplants, which are important in treating a number of diseases like cancer. Over 30 million people around the world have volunteered to join a registry and had their HLA genes typed.

In bone marrow stem cell transplantation, closer HLA matching between donor and recipient reduces the risk of graft-versus-host disease, where the recipient’s new immune system recognizes the new body it is in as foreign. By analyzing HLA frequencies in global populations, the lab uses this information to inform algorithms that identify the best match in large registries. The lab is now working to adapt



Population Genetics & Informatics for Transplantation

Algorithms for Transplantation ... (continued)

large HLA datasets and informatics tools developed originally for stem cell matching for new applications in solid organ transplantation. In kidney transplantation, closer HLA matching reduces the likelihood of developing antibodies that lead to organ rejection. Currently, kidneys are matched at a broad HLA antigen level, rather than the more specific allele level defined by HLA molecular typing assays.

Then lab created bioinformatics tools for streamlining the process of getting molecular typing into the kidney allocation system – and is well-positioned to help bridge the US Stem Cell Registry “Be The Match” program and the United Network for Organ Sharing, which manages the national organ allocation system. By working together with these outside stakeholders, they improve transplant outcomes for all organ and tissue recipients.

Cancer Development & Immunotherapy Treatment

HLA molecules are also important in the body’s natural defenses against cancer. Cancerous cells are able to survive in the human body by evading the immune system. Some HLA alleles are better at helping the immune system detect certain types of mutations in cancerous cells, shaping the evolution of tumors.

The Lab uses large stem cell registry datasets from “Be The Match” to identify which HLA alleles influence the risk of developing blood diseases like leukemias and lymphomas treated by bone marrow transplantation. HLA genes also influence the risk of developing autoimmune diseases, such as severe aplastic anemia. Recently, cancer immunotherapy has become more and more prevalent in the fight against cancer, and currently indicates that HLA variants are also associated with response to immunotherapy. Understanding how the immune system uses HLA to fight cancer will ultimately optimize immunotherapy regimens.

The Gragert Lab is dedicated to using advanced large data set analysis to better understand the role of HLA molecules in improving outcomes for some of the most catastrophic human diseases, and available for collaborative opportunities to advance this area of science and treatment.

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